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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	PAPER NUMBER
1614	

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11/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/889,251	NAVIAUX	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67,70,73-81,84-91 and 95-180* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67,70,73-81,84-91,95-109, 111-179* is/are rejected.

7)☒ Claim(s) *110 and 180* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's Amendment filed July 17, 2007 is acknowledged. New claims 111-180 are presented. Accordingly, claims 67, 70, 73-81, 84-91 and 95-180 are now under consideration.

Clarification is requested concerning Applicant's reference in the Remarks section of the Communication filed July 17, 2007 drawn to an Overland et al. reference.

In the last Office Action claims 67, 70, 73-80, 81, 84-89, 91 and 96-108 were rejected under 35 U.S.C. 102(e) as being anticipated by Nagley et al., U.S. Patent 5,981,601. It was asserted Nagley teaches the administration of uridine, including functional derivatives and/or precursors thereof, to treat mitochondrial disorders wherein at least one mutation in the mitochondria has occurred. Primarily, Nagley's teaching is drawn to the mitochondrial toxicity and physiologic effects that result from the administration of the of the reverse transcriptase inhibitor drug AZT. See claims 1, 5, 6, 10 and 18, column 18-20 and 24. AZT acts as a mitochondrial poison in that it causes cellular cytotoxicity, which is particularly manifest in muscle, causing myopathy. As a mitochondrial poison, AZT disrupts mitochondrial respiratory chain function resulting in a reduced capacity for generating ATP. As required by instant claims 85, 86, 104 and 105, the administration of uridine may be accompanied by the administration of one or more co-factors or vitamins, such as coenzyme Q or an antioxidant as ascorbic acid. See Example 1, column 11. See column 5, lines 50-55, where Nagley's claimed redox compounds may include vitamins of the K series or ascorbic acid. See column 3, lines 50-60. Anti-oxidant scavengers include α-lipoic acid, as recited in instant claims 87 and 106. Further, other diseases associated with disruption of the mitochondrial respiratory chain function are also included in Nagley's teaching. See column 8, line 63, to column 9, line 10, where encephalomyopathy lactic

acidosis is included among those mitochondrial pathologies contemplated. As required by instant claims 88, 89, 107 and 108, see column 7, lines 3-5, where the disclosed daily dosage range overlaps with those instantly claimed. The claimed recitation "about 2 gm/m^2 overlaps with Nagley's teaching of 2000 mg per day.

Functional limitations are recited in instant claims 74-79, 84, 96-100, 102 and 103. The claims are drawn to deficiencies of cardiolipin, of a pyrimidine synthetic pathway, of the uridine synthetic pathway, of the expression and/or activity of an enzyme in the pyrimidine synthetic pathway, such as dihydroorotate dehydrogenase or uridine monophosphate synthetase, and of lower than normal uridine levels. In the absence of a showing that these mechanisms of action are not present in a mitochondrial disorder, one skilled in the art would have considered such deficiencies to be inherent in the pathogenesis of the disease processes.

Applicant's entire response is drawn to claims 67 and 91 wherein Applicant argues "every element of claims 67 and 91" is not disclosed by Nagley.

Applicant argues Nagley fails to explicitly teach or inherently describe any of the specific diseases recited in claims 67 and 91, particularly with regard to the recitations "encephalomyopathy" and "renal tubular acidosis" in these claims. Although Applicant states on page 23 of the Communication filed July 17, 2007 that "encephalomyopthy" - which is the exact term claimed – is **broader**, Applicant urges these conditions differ from "encephalomyopathy lactic acidosis."

Applicant's argument is not persuasive. Nagley's teaching is directed to mitochondrial dysfunction. For example, Nagley states mitochondrial poisons directly or indirectly disrupt mitochondrial respiratory chain function. As required by instant claims 80, 81, 101, 102

120, 121, 136, 137, 155, 156, 171 and 172, the mitochondrial disorder is the result of prior administration of a pharmaceutical agent. The pharmaceutical agent is the anti-retroviral agent AZT, a reverse transcriptase inhibitor and a mitochondrial poison. AZT exhibits cellular cytotoxicity which is particularly manifest in muscle and causes **a** myopathy. In particular, AZT affects the oxidation/phosphorylation system and the activity of complex I, III and IV of the mitochondrial respiratory chain. Given their broadest reasonable interpretation, and in view of the teachings of Nagley, the recited terms in claims 67 and 91 "lactic acidemia" and "encephalopathy" clearly encompass encephalopathy lactic acidosis. Nagley teaches encephalopathy lactic acidosis to be an example of a disease associated with disruption of mitochondrial respiratory chain function. The rejection of record of claims 67, 70, 73-81, 84-89, 91 and 96-108 under 35 U.S.C. 102(e), as being anticipated by Nagley et al., U.S. Patent 5,981,601, is maintained and is presently extended to include new claims 111-127, 129, 131-143, 146-162, 164, 166-178. (Applicant's comment on page 25 of the Communication filed July 17, 2007 drawn to the "transitional clause consisting of" is noted. However, in independent claims 111 and 129, only the claimed pharmaceutical composition consists of components (a) and (b). The actual administration is still open to additional administrations, which may be a compound.)

Claims 67, 70, 73-81, 84-91 and 96-109 were rejected under 35 U.S.C. 103(a) in the last Office Action as being unpatentable over Nagley et al., U.S. Patent 5,981,601, in view of Page et al., Proc. National Academy of Sciences. It was asserted although Nagley fails to teach the administration of uridine in a daily dosage of about 6.0 g/m^2, Page teaches the safe and effective

administration of higher doses of uridine that approach about 6.0 g/m^2. See page 1603, column 2.

Applicant agrees Page teaches such dosages, but argues the combination of references fails to teach or suggest all of the limitations recited in claims 67 and 91. Applicant further discusses the tenets of the *KSR International v. Teleflex Inc.* (2007) decision.

The Page reference is applied merely to show the claimed dosage of uridine is established in the prior art to be safe and effective for the treatment of inborn errors of metabolism. Accordingly, one may consider the inclusion of the Page reference to supply a general state of the art with respect to safe and effective uridine dosing, and the reference augments an expectation of success in treating mitochondrial diseases.

The rejection of record of claims 67, 70, 73-81, 84-91 and 96-109 under 35 U.S.C. 103(a) as being unpatentable over Nagley et al., U.S. Patent 5,981,601, in view of Page et al., Proc. National Academy of Sciences , in maintained for the reasons of record. The rejection is presently extended to include new claims 111-179.

Claims 67, 70, 73-81, 84-90, 95-109, 111-163 and 165-179 are rejected under 35 U.S.C. 112, first paragraph, as lacking a clear written description of the invention and of the manner and process of practicing it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice same, and, as not setting forth the best mode contemplated by the inventor to carry out the invention.

Independent claims 67, 111 and 146 are directed to a treatment of a mitochondrial disorder for a subject "at risk of having such disorder." The specification provides support for those patients suffering from mitochondrial disorders in Examples 1-5 on pages 14-19 of the

specification. However, one skilled in the art finds no guidance with respect to patients at risk for mitochondrial disorders comprising administering the L- or D-isomer of a keto tautomer or an enol tautomer of Formula I or IA, respectively. Accordingly, Claims 67, 111 and 146 do not find support in the specification in the form of a definitive treatment for this potential patient population. There is no showing that Applicant had possession of the claimed invention in this regard. The present level of skill in the neurology art for treating mitochondrial disorders is immature and would reasonably require a more detailed written description directed to the means of carrying out the claimed methods involving risk for developing the disease.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached from 10:30 to 7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 3, 2007

Phyllis Spivack

Phyllis Spivack
PHYLLIS SPIVACK
PRIMARY EXAMINER

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